A voltage-sensing phosphatase, Ci-VSP, which shares sequence identity with PTEN, dephosphorylates phosphatidylinositol 4,5-bisphosphate.

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Public Summary:

Scientific Abstract:
Phosphatidylinositol lipids play diverse physiological roles, and their concentrations are tightly regulated by various kinases and phosphatases. The enzymatic activity of Ciona intestinalis voltage sensor-containing phosphatase (Ci-VSP), recently identified as a member of the PTEN (phosphatase and tensin homolog deleted on chromosome 10) family of phosphatidylinositol phosphatases, is regulated by its own voltage-sensor domain in a voltage-dependent manner. However, a detailed mechanism of Ci-VSP regulation and its substrate specificity remain unknown. Here we determined the in vitro substrate specificity of Ci-VSP by measuring the phosphoinositide phosphatase activity of the Ci-VSP cytoplasmic phosphatase domain. Despite the high degree of identity shared between the active sites of PTEN and Ci-VSP, Ci-VSP dephosphorylates not only the PTEN substrate, phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P3], but also, unlike PTEN, phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2]. Enzymatic action on PI(4,5)P2 removes the phosphate at position 5 of the inositol ring, resulting in the production of phosphatidylinositol 4-phosphate [PI(4)P]. The active site Cys-X(5)-Arg (CX(5)R) sequence of Ci-VSP differs with that of PTEN only at amino acid 365 where a glycine residue in Ci-VSP is replaced by an alanine in PTEN. Ci-VSP with a G365A mutation no longer dephosphorylates PI(4,5)P2 and is not capable of inducing depolarization-dependent rundown of a PI(4,5)P2-dependent potassium channel. These results indicate that Ci-VSP is a PI(3,4,5)P3/PI(4,5)P2 phosphatase that uniquely functions in the voltage-dependent regulation of ion channels through regulation of PI(4,5)P2 levels.

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